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Review Article

A COMPREHENSIVE REVIEW ON ANTIOXIDANTS

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ABSTRACT

This present review mainly focused on providing a brief and latest information on antioxidants its classification, antioxidants role in human body, pharmacology of antioxidants, benefits, list of foods which contain high antioxidant content and effects that causes due to overdose of antioxidants. All living organisms utilize oxygen to metabolize various substances and use the dietary nutrients in order to produce energy for survival. Oxygen thus is a vital component for all living aerobic organisms. Antioxidants are man-made or natural substances that may prevent or delay some types of cell damage, such as that caused by free radicals. Each of the living organisms thus have a complex network of antioxidant metabolites and enzymes that act together to prevent oxidative damage to cellular components such as DNA, proteins and lipids. These systems of antioxidants prevent these reactive oxygen species (ROS) species from being formed or remove them before they can damage vital components of the cell.

INTRODUCTION

All living organisms utilize oxygen to metabolize various substances and use the dietary nutrients in order to produce energy for survival. Oxygen thus is a vital component for all living aerobic organisms. Oxygen meditates chemical reactions that metabolize fats, proteins, and carbohydrates to produce energy. Oxidation is a chemical reaction that can produce free radicals, leading to chain reactions that may damage cells. Antioxidants are substances that protect cells from the damage caused by free radicals. A free radical is a unstable molecules made by the process of oxidation during normal metabolism. These free radicals are capable of attacking the healthy cells of the body. Free radicals may play a part in cancer, heart disease, stroke, and other diseases of aging.[1]

Free radicles are unstable as they contain unpaired electrons and reach out and capture electrons from other substances in order to neutralize themselves. This initially stabilizes the free radical but generates another in the process. Soon a chain reaction begins and thousands of free radical reactions can occur within a few seconds on the primary reaction.[2]

Each of the living organisms thus have a complex network of antioxidant metabolites and enzymes that act together to prevent oxidative damage to cellular components such as DNA, proteins and lipids. These antioxidant systems prevent the formation of reactive oxygen species(ROS) or remove them before they can damage vital components of the cell.[3]

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Definition

Antioxidants are man-made or natural substances that may prevent or delay some types of cell damage, such as that caused by free radicals.[4]

Classification of Antioxidants

Antioxidants are classified based on their food source, nature of solubility, how they work, source i.e., natural or synthetic.

Classification of antioxidants based on their source

Antioxidants can be classified into two major types based on their source, i.e.,
natural antioxidants and
synthetic antioxidants.

Natural Antioxidants

Natural antioxidants are either synthesized in human body through various metabolic process or taken in the form of diet and their activity depends upon their physical and chemical properties.[5] Natural antioxidants are further divided into two types. They are

- enzymatic antioxidants and
- nonenzymatic antioxidants

Enzymatic Antioxidants

These enzymatic antioxidants are produced in the human body and the breakdown of the superoxide radicals which are formed during oxygen metabolism done by various enzymes. Some key enzymes are Superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase.[6] Enzymatic antioxidants are again subdivided into

- Primary antioxidant and
- Secondary antioxidant.

Primary Antioxidants

- Superoxide dismutase (SOD),
- Glutathione peroxidase (GPx)
- catalase enzymes

Superoxide Dismutase

It is found in both the dermis and the epidermis. It removes the superoxide radical (O–) and repairs the body cells damaged by free radical. SOD catalyzes the reduction of superoxide anions to hydrogen peroxide. SOD is also known to compete with nitric oxide (NO) for superoxide anion, which inactivates NO to form peroxynitrite[7]. Therefore, by scavenging superoxide anions, it promotes the activity of NO.

Catalase enzyme (CAT)

It is found in the blood and most of the living cells and decomposes H2O2 into water and oxygen. Catalase with glucose peroxidase is also used commercially for the preservation of the fruit juices.8

$$2H_2O_2 \xrightarrow{CAT} 2H_2O + O_2$$

Glutathione peroxidase (GPx)

It is a group of seleniumdependentenzymes, anditis found in body cells. GPxcatalyzes the reaction of H_2O_2 by reduction of glutathione (GSH), oxidized glutathione (GSSG) is produced.[9]

$$2GSH + H_2O_2 \xrightarrow{GP_x} GSSG + 2H_2O$$

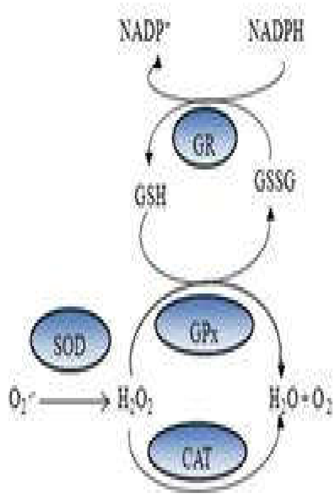

Fig 1 Outline of the mechanism of enzymatic antioxidants in the removal of free radical

Secondary Antioxidant

- glutathione reductase (GR)
- glucose-6-phosphate dehydrogenase (G6PDH).

G6PDH generates NADPH. GR is required to recycle the reduced glutathione (GSH) using secondary enzyme GR and NADPH.

$$GSSG + NADPH \xrightarrow{GR} NADP + 2GSH$$

Nonenzymatic Antioxidants

They are a class of the antioxidants which are not found in the body naturally but are required to be supplemented for the proper metabolism. Some of the known nonenzymatic antioxidants are minerals, vitamins, carotenoids, polyphenols, and other antioxidants as listed below.10

Minerals

Minerals are required in the body cells for the proper functioning of the enzymes. If there is any deficiencyin them, it is known to affect the metabolism of many macromolecules. They include selenium, copper, iron, zinc, and manganese. They act as cofactors for the enzymatic antioxidants. These metal ions react with superoxide dismutase enzyme and helps in breakdown of superoxide radicals.[11]

- $M^{(n+1)+}\text{-SOD} + O_2^- \rightarrow M^{n+}\text{-SOD} + O_2$
- $M^{n+}\text{-SOD} + O_2^- + 2H^+ \rightarrow M^{(n+1)+}\text{-SOD} + H_2O_2$.

where M = Cu (n=1) ; Mn (n=2) ; Fe (n=2) ; Ni (n=2).
In the above first reaction, reduction of metal ions and oxidation of superoxide radical takes place, where as in the second reaction oxidation of metal ions and reduction of superoxide radical takes place.[12]

Vitamins

Vitamins form the class of micronutrients required for the proper functioning of the body's antioxidant enzyme system, such as vitamin A, vitamin C and vitamin E. They cannot be synthesized in our body and hence need to be supplemented in the diet.

Table 1 different vitamins, their sources and their action in prevention of radical formation

Vitamins	Source	Prevention of radical formation
Vitamin A	Sweet potatoes, carrots, milk, egg yolks, and mozzarella cheese	It assists immune system and is found in three main forms: retinol, 3,4-didehydroretinol, and 3-hydroxyretinol.
Vitamin C	Fruits (mainly citrus), vegetables, cereals, beef, poultry, fish.	It is helpful in preventing some of the DNA damage caused by free radicals, which may contribute to the aging process and the development of diseases, such as cancer, heart disease, and arthritis.
Vitamin E	Almonds, sunflower oil, soybean oils, oil of wheat germs, nuts, broccoli, fish oil.	α-tocopherol is the most important lipid-soluble antioxidant which reacts with the lipid radical and protects the membranes from lipid peroxidation which results in the formation of oxidized α-tocopheroxyl radicals that can be recycled to the reduced form through reduction by other antioxidants, such as ascorbate and retinol.

Carotenoid

Carotenoid consists of β-carotene, lycopene, lutein, and zeaxanthin. They are fatsolublecolored compounds found in fruits and vegetables. Lutein is best known for its role in protection of retina against harmful action of free radicals and also prevents atherosclerosis. Although lycopene, lutein and zeaxanthin do not possess provitamin A activity, β-carotene is known as a precursor for vitamin A[12]. Tomato is a good source of lycopene and spinach is a good source of zeaxanthin. It has been shown that lycopene is a potent antioxidant and is the most effective compound in removing singlet oxygen found in tomatoes, watermelon, guava, papaya, apricots, pink grapefruit, and other foods.[13]

Polyphenols

Polyphenols is a class of the phytochemicals that possess marked antioxidant activities. Their antioxidant activities depend on their chemical and physical properties which in turn regulates the metabolism depending on their molecular structures. Poly phenols consists of phenolic acids, flavonoids, gingerol, curcumin.

Flavonoid is a major class of polyphenolic compound and is mostly found in vegetables, fruits, grains, seeds, leaves, flower, bark, etc. Some of the spices, such as ginger and turmeric, are also good sources of polyphenolic compound, e.g., gingerol is obtained from the rhizomes of ginger, whereas curcumin is the main bioactive component of turmeric and is known to possess good antioxidant activity. Curcumin is an excellent scavenger of ROS, such as O_2 radicals, lipid peroxyl radicals (LO_2), OH radicals, and nitrogen dioxide (NO_2) radicals, which induced oxidative stress. Curcumin has been shown to inhibit lipid peroxidation and has been shown to increase GSH levels also in epithelial cells which lead to lower ROS production.[14]

concentrations in invitro model and is regarded as the best antioxidant against lipid peroxidation.

Uric Acid

Uric acid is a powerful antioxidant and is a scavenger of singlet oxygen and radicals. Urate reduces the oxo-heme oxidant formed by peroxide reaction with hemoglobin and protects erythrocytes from peroxidative damage.[17]

Coenzyme Q

Coenzyme Q is also known as ubiquinol (Co Q) and is an oil-soluble antioxidant. This is produced in the body through monovalent pathway, in heart, liver, kidney, pancreas, etc. The mechanism of the action may occur in two ways:

In the first mechanism, reduced form of ubiquinol (CoQH) acts as chain-breaking antioxidant and reduces peroxyl (ROO.) and alcoxyl radicals (LO).[18]

$$CoQH + ROO \xrightarrow{yields} Q + ROOH$$

In the second mechanism, it reacts with vitamin E radical (TO.) and yields carboxyl group

$$CoQH + TO \xrightarrow{yields} Q + ROOH$$

Table 2 Different types of polyphenols and their action

Broad classification	Sub-category	Typical plant	Typical actions
Polyphenols	Anthocyanins	Blueberry	Reduces eye strain, improves reduced vision, improves liver function
isoflavone	-	soybeans	Improves menopause disorders Prevents osteoporosis
catechin	-	tea	Antibacterial effects, anti-inflammatory effects
Rutin	-	*Soba* buckwheat noodles	Improves arteriosclerosis
Terpenoid	Rikopin	tomotoes	Prevents cancer, suppresses arteriosclerosis
lutein	-	Spinach	(Effective against) Macular degeneration
sulforaphane	-	Broccoli	Neutralizes of carcinogenic substances, kills pylori bacteria, promotes metabolism
beta-glucan	-	Agaricus	Immune activation action
Organic sulfur compounds	Allicin	Onions	Prevents arteriosclerosis, reduces fatty deposits
Sugar-related compounds	Saponin	soyabeans	Suppresses cholesterol absorption
Long-chain alkylphenol derivatives	Capsaicin	Cayenne pepper	Promotes metabolism

Other Antioxidants

Transition Metal-Binding Proteins

Albumin, ceruloplasmin, hepatoglobin, and transferrin are the transition metal-binding proteins found in human plasma. They bind with transition metals, a0nd control the production of metal catalyzed free radicals. Albumin and ceruloplasmin are the copper ion sequesters, hepatoglobin is hemoglobin sequester, and transferrin acts as free iron sequester.[15]

Nonprotein Antioxidants

Bilirubin, uric acids, and ubiquinol are nonprotein antioxidants which inhibit the oxidation processes by scavenging free radicals.[16]

Bilirubin

Bilirubin is an end product of heme catabolism. It is a lipid-soluble cytotoxic product that needs to be excreted. However, bilirubin efficiently scavenges peroxyl radical at micromolar

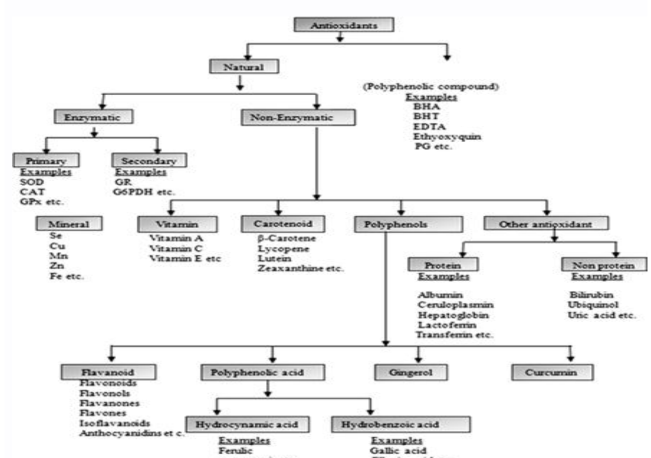

Fig 2 Flowchart of classification of antibiotics

Classification of antioxidants based on their food source

These antioxidants are classified into two types based on their food source. They are

- Primary antioxidants or type I
- Secondary antioxidants (type II)

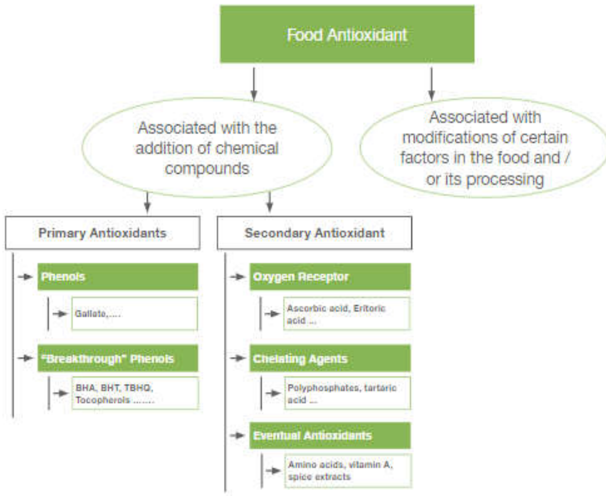

Fig 3 Food antioxidants and its types

Primary antioxidants or type I: Primary antioxidants are capable of donating hydrogen atom to the free radical for the generation of more stable radical which can break the chain reaction of oxidation.[19]

$$R^{\cdot} + AH \longrightarrow RH + A^{\cdot}$$
$$RO^{\cdot} + AH \longrightarrow ROH + A^{\cdot}$$
$$ROO^{\cdot} + AH \longrightarrow ROOH + A^{\cdot}$$
$$R^{\cdot} + A^{\cdot} \longrightarrow RA$$
$$RO^{\cdot} + A^{\cdot} \longrightarrow ROA$$
$$A^{\cdot} + X \longrightarrow \text{Non-radical Compound}$$

The addition of these compounds to food should, by itself, imply an increase in the induction period, as shown in the following table.

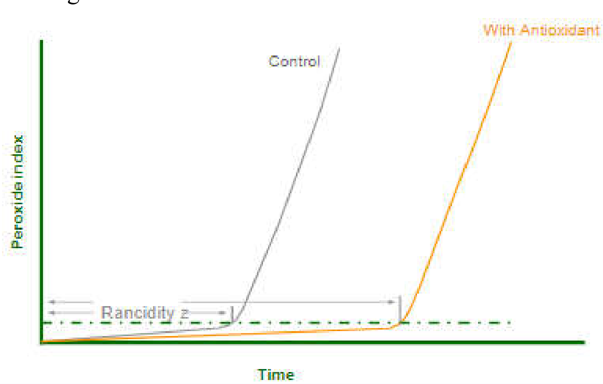

Fig 4 Effect of an antioxidant on the development of oxidation

This increase is directly related to the amount of antioxidant added up to a certain concentration, since, sometimes with higher proportions, an opposite effect is achieved, as shown in the following table.

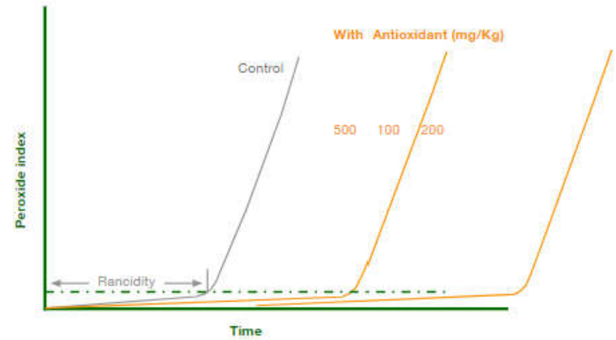

Fig 5 Effect of an antioxidant on the development of oxidation

The effectiveness of the activity of these antioxidants depends both on the antioxidant itself and on the medium in which it acts. It is necessary to know the exact moment of the incorporation of the antioxidant since if the oxidation process is advanced, the antioxidant loses its capacity of action.[20]
Among the main primary antioxidants include:

Phenolic antioxidants

In this type, antioxidants are phenolic type hydrogen donors, and are able to effectively move an unpaired electron.

The main antioxidants of this type are:

- Propyl gallate (E-310): Occasionally, Propyl Galato acts together with synthetic and natural antioxidants. It is important to bear in mind that it is a substance that is sensitive to high preparation temperatures.
- Octylgallate (E-311): It is used as a synthetic antioxidant in fats and water, where it is sometimes included to prevent rancidity in oils.
- Dodecyl gallate (E-312): It is used as a synthetic antioxidant in fats and beverages, particularly to prevent rancidity in oils.

Galactose, BHA and BHT were used together in oils, with the exception of olive oil. They are also used in canned and semi-preserved fish and processed cheese, pastry or confectionery, cookies.[21]

Breakthrough phenols

The main antioxidants of this type are:

Butyl-hydroxy-anisole (BHA, E-320): It is one of the most common antioxidants in human nutrition. Chemically, BHA is a mixture of two isomers: 2-tert-butyl-4-hydroxyanisole and 3-tert-butyl-4-hydroxyanisole. The second one is generally considered as a better antioxidant, and represents 90% of commercial BHA.[22]

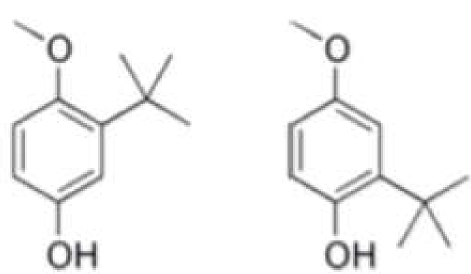

Fig 6 structure of BHA,E-320

This antioxidant is effective primarily in animal fats and more discreetly in vegetable fats and oils. However, due to the chemical structure they present, they are extremely volatile at baking and frying temperatures.

Butyl-hydroxy-toluol (BHT, E-321): Together with BHA, they are the most used antioxidants in human nutrition. BHT (3,5-di-tert-butyl-4-hydroxytoluene) is an appropriate antioxidant for heat treatment, although it is not so stable.[23]

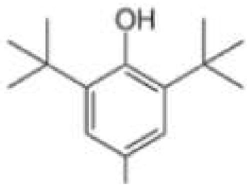

Fig 7 structure of BHA,E-321

It is commonly used in combination with BHA to provide increased antioxidant activity. It is also commonly used together with other antioxidants, such as propyl gallate and citric acid, for the stabilization of oils and high-fat foods.[24]

Both BHA and BHT have a slight phenolic odor when used at high temperature for a prolonged period of time.

- ***Terbutil hydroquinone (TBHQ, E-319):*** TBHQ is used in vegetable oils and animal fats. As an antioxidant, TBHQ is more effective in vegetable oils than BHA and BHT. It is heat-stable and very useful in the prevention of oxidation of frying oils.[25]
- ***Tocopherols (E-306):*** Tocopherols is the antioxidant extracted from nature and is used most commonly in the food industry. It is completely fat-soluble and does not alter the organoleptic properties of the food. It is also safe, effective and easy to incorporate. Thetocopherols are formed by four isomers (Alpha, Beta, Gamma and Delta) with different antioxidant and vitamin activities. After several exhaustive studies, it has been shown that the main antioxidant activity is produced by the Gamma and Delta isomers. In products formed by structures with double bonds more input of tocopherols is needed, since the unsaturated substances are more sensitive to oxidation.[26]

Secondary antioxidants (type II)

Secondary antioxidants (type II) are those that delay oxidation through other mechanisms, such as metal chelation, the regeneration of primary antioxidants, the decomposition of hydroperoxides and the elimination of oxygen, among others.[27]

Classificaion of antioxidants based on their nature of solubility

- ***Water-soluble:*** Water-soluble antioxidants work their magic on the the blood plasma surrounding the cells
- ***Fat-soluble:*** Fat-soluble ones work their magic on the cell membrane, which is made of mainly fats and lipids, and on the surrounding lipids.
- ***Both water-soluble and fat-soluble:*** Those that are both Water- and Fat-soluble, are required to work their magic on the cells - on the cell membranes, mainly fats and lipids, and on the inside of the cells, as the cells contain water. Being Water-soluble alone will not be able to penetrate the cell membranes, so we need ones that are both Water and Fat-soluble! - using their fat-soluble characteristic they can move into the cells, and then unleash their water-soluble character.[28]

Classification of antioxidants based on how they work

Based on how they work antioxidants are divided into 4 types. They are secondary antioxidants (type II) are those that delay oxidation through other mechanisms, such as metal chelation, the regeneration of primary antioxidants, the decomposition of hydroperoxides and the elimination of oxygen, among others.[29]

- Preventative antioxidants
- Chain Breaking antioxidants

Preventative antioxidants: Some work by preventing the oxidative process before it can begin such as, the antioxidant enzymes (produced by the body) or hydrogen from hydrogen enriched water.[30]

Chain Breaking antioxidants: Some (or most) work through neutralizing the free radicals by donating their electron to the free radical, and in the process becomes a free radical but of a lesser potent nature. And then this created free radical is then "saved" by another antioxidant, and the process continues until the "diluted" free radical is no longer a treat to our cells.[31]

Reactive oxygen species (ROS)

ROS is a term which encompasses all highly reactive, oxygen-containing molecules, including free radicals. Types of ROS include the hydroxyl radical, hydrogen peroxide, the superoxide anion radical, nitric oxide radical, singlet oxygen, hypochlorite radical, and various lipid peroxides. These can react with membrane lipids, nucleic acids, proteins and enzymes, and other small molecules.[32]

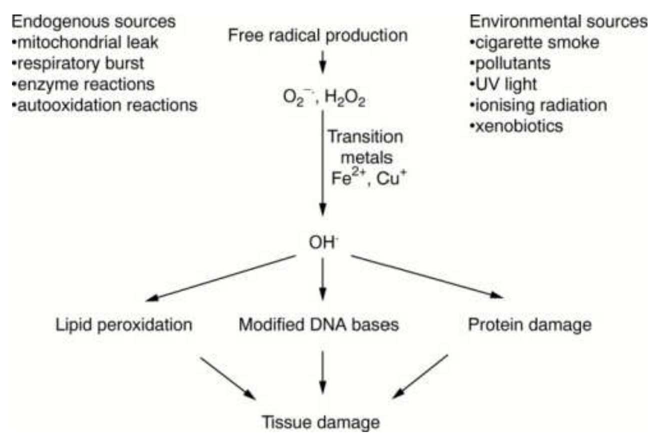

Fig 8 mechanism of ROS and how it damges cell[33]

Oxidation stress

Oxidative stress means an unbalance between pro-oxidants and antioxidant mechanisms. This results in excessive oxidative metabolism. This stress can be due to several environmental factors such as exposure to pollutants, alcohol, medications, infections, poor diet, toxins, radiation etc. Oxidative damage to DNA, proteins, and other macromolecules may lead to a wide range of human diseases most notably heart disease and cancer.[34]

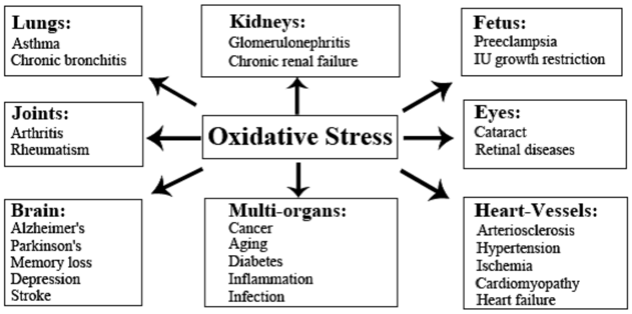

Fig 9 various diseases caused by oxidative stress[35]

Role of antioxidants in body

Apart from diet, the body also has several antioxidant mechanisms that can protect itself from ROS mediated damage. The antioxidant enzymes - glutathione peroxidase, catalase, and superoxide dismutase (SOD) are such enzymes. They require micronutrient cofactors such as selenium, iron, copper, zinc, and manganese for their activity. It has been suggested that an inadequate dietary intake of these trace minerals may also lead to low antioxidant activity.[36]

Antioxidants and Skin Health Benefits

When skin is exposed to high levels of radiation emitted from the sun i.e., ultraviolet light, photo-oxidative damage is induced by the formation of different types of reactive species of oxygen, including singlet oxygen, superoxide radicals, and peroxide radicals. These forms of reactive oxygen causes damage to cellular lipids, proteins, and DNA, and they are considered to be the primary contributors to erythema (sunburn), premature aging of the skin, photodermatoses, and skin cancers.[37] Astaxanthin, followed by beta-carotene combined with vitamin E has been shown to be one of the most powerful antioxidant combinations for helping protect the skin from reactive species of oxygen.

Antioxidants and Immune System Support

Singlet oxygen has the ability to catalyze production of free radical and can compromise the immune system. Astaxanthin and Spirulina have been shown to enhance both the non-specific and specific immune system, and protects the cell membranes and cellular DNA from mutation. Astaxanthin is the single most powerful quencher of singlet oxygen, and is up to ten times stronger than other carotenoids (including beta-carotene), and up to 500 times stronger than alpha tocopherol (Vitamin E), while Spirulina has a variety of antioxidants and other substances that are beneficial in boosting immunity.[38]

Cardiovascular Disease

The role of free radicals in the development of heart disease has been a topic of considerable interest and attention. High levels of plasma cholesterol, particularly LDL cholesterol, is one of the risk factors linked to the development of atherosclerosis. Data from several studies suggest that LDL is oxidatively modified by free radical reactions and that this oxidized low density lipoprotein plays an important role in the initiation of the atherogenic process, allowing its infiltration into the vessel wall. In France there is regular consumption of moderate amounts of wine and other alcoholic beverages which causes an increase in high density lipoprotein cholesterol, which is considered antiatherogenic. Red wine is also rich in flavonoids, which are more potent as antioxidants than vitamin E is, and it is suggested that these compounds contribute substantially to the reduction of mortality from coronary heart disease in France.[39]

The beneficial effects of antioxidants have been studied experimentally in rabbits, and the results suggest that protecting LDL from oxidation slows the progression of the atherosclerotic process. Probucol is a drug that reduces plasma cholesterol and also serves as an antioxidant. It is carried by LDL and essentially prevents its oxidation. In hypercholesterolemic rabbits, probucol retarded the progression of atherosclerotic lesions by 50% compared with those in a control group that had cholesterol levels lowered to comparable levels with lovastatin, which is not an antioxidant.

Brain

The brain and central nervous system seem to be particularly susceptible to free-radical mediated damage. Polyunsaturated fatty acids, substrates for lipid peroxides, are major constituents of cell membranes, and in addition some brain cells contain higher concentrations of iron, which promotes cytotoxic radical formation.

Amyotrophic lateral sclerosis is a progressive degenerative disorder of motor neurons in the spinal cord, brain stem, and motor cortex characterized by varying degrees of weakness, atrophy, fasciculation, and spasticity. It has recently been established that this disease is linked to defects in the SOD' gene, which encodes the cytosolic SOD. Superoxide radical formation in brain leads to parkinson's disease, Alzheimer's disease and Down's syndrome.[40]

Reperfusion Injury

Temporary interruption of blood to tissues causes damage to those tissues and is assumed to occur as a result of depletion of adenosine triphosphate during the period of hypoxia. If the duration of ischemia does not do irreversible damage, tissue function can be salvaged by reperfusion. Although other factors may be involved,41 most researchers agree that free radicals play a major role in the pathogenesis of reperfusion injury. During the first 30 to 60 seconds of postischemic reperfusion, there is generation of superoxide, which can combine with iron released by hypoxic cells to form hydroxyl radical, the initiator of lipid peroxidation.42 Studies in isolated organs showed that tissue function is better preserved if antioxidants are incorporated in the reoxygenation medium at the end of the ischemic period. Inhibition of lipid peroxidation after ischemia and reperfusion accordingly protects tissues such as the heart.[41]

Cataracts

Cataracts are a condition in which opaque regions develop within the normally transparent lens of the eye, resulting in significant loss of visual activity. It is one of the major causes of age dependent, visual impairment and blindness. The intraocular generation of oxygen radicals may constitute one of the significant risk factors in cataractogenesis. Hydrogen peroxide is present (20 to 30 [tmol/L) in the aqueous humor and can give rise to hydroxyl radicals. Epidemiologic and experimental studies suggest that antioxidants maybe therapeutically useful against this disease. Vitamin C is of particular interest because of the high levels of ascorbic acid (30-fold to 35-fold over plasma level) in the human lens. There is reduced risk of senile cataracts with an increased intake of vitamin C as well as of other antioxidants such as beta carotenes and vitamin E.[42]

Sources of antioxidants

Based on their Oxygen Radical Absorbance Capacity (ORAC) values the top 10 good sources of antioxidants present in food.

1. Goji berries: 4,310 ORAC score
2. Wild blueberries: 9,621 ORAC score
3. Dark chocolate: 20,816 ORAC score
4. Pecans: 17,940 ORAC score
5. Artichoke (boiled): 9,416 ORAC score
6. Elderberries: 14,697 ORAC score
7. Kidney beans: 8,606 ORAC score
8. Cranberries: 9,090 ORAC score
9. Blackberries: 5,905 ORAC score
10. Cilantro: 5,141 ORAC score

The ORAC scores above are based on weight. This means that it might not be practical to eat high amounts of all of these antioxidant foods. Other high antioxidant foods not listed above, which are still great sources and highly beneficial, include common foods like Brown rice, watermelon, ripe banana, coffee, oats, black tea, tomatoes, carrots, pumpkin seeds, sweet potatoes, fish, lemon, pomegranates, strawberries, kale, broccoli, grapes or red wine, squash, egg and wild-caught salmon. Try to consume at least three to four servings daily of these high antioxidant foods (even more is better) for optimal health.[43]

Along with antioxidant foods, certain herbs, spices and essential oils derived from nutrient-dense plants are extremely high in healing antioxidant compounds. Here is another list of the herbs you can try adding to your diet for increased protection against disease. Many of these herbs/spices are also available in concentrated essential oil form. Look for 100 percent pure (therapeutic grade) oils, which are highest in antioxidants.

1. Clove:314,446 ORAC score
2. Cinnamon: 267,537 ORAC score
3. Oregano: 159,277 ORAC score
4. Turmeric: 102,700 ORAC score
5. Cocoa: 80,933 ORAC score
6. Cumin: 76,800 ORAC score
7. Parsley (dried): 74,349 ORAC score
8. Basil: 67,553 ORAC score
9. Ginger: 28,811 ORAC score
10. Thyme: 27,426 ORAC score

Along with antioxidant foods and herbs, there are certain antioxidant supplements that decreases the superoxide radical formation and is mostly available in market.[44]

Glutathione

Glutathione is considered the body's most important antioxidant because it's found *within* the cells and helps boost activities of other antioxidants or vitamins. Glutathione is a peptide consisting of three key amino acids that plays several vital roles in the body, including helping with protein use, creation of enzymes, detoxification, digestion of fats and destruction of cancer cells.[45]

Quercetin

Derived naturally from foods like berries and leafy greens, quercetinseems to be safe for almost everyone and poses little risks. Most studies have found little to no side effects in people eating nutrient-dense diets high in quercetin or taking supplements by mouth short term.[46]

Amounts up to 500 milligrams taken twice daily for 12 weeks appear to be very safe for helping manage a number of inflammatory health problems, including heart disease and blood vessel problems, allergies, infections, chronic fatigue, and symptoms related to autoimmune disorders like arthritis.

Lutein

Lutein has benefits for the eyes, skin, arteries, heart and immune system, although food sources seem to be generally more effective and safer than supplements. Some evidence shows that people who obtain more lutein from their diets experience lower rates of breast, colon, cervical and lung cancers.[47]

Vitamin C

It is Known for improving immunity, vitamin C helps protect against colds, the flu, and potentially cancer, skin and eye problems.[48]

Resveratrol

Resveratrol is an active ingredient found in cocoa, red grapes, and dark berries, such as lingonberries, blueberries, mulberries and bilberries. It's a polyphonic bioflavonoid antioxidant that's produced by these plants as a response to stress, injury and fungal infection, helping protect the heart, arteries and more.[49]

Astaxanthin

Astaxanthin is found in wild-caught salmon and krill and has benefits like reducing age spots, boosting energy levels, supporting joint health and preventing symptoms of ADHD.[50]

Selenium

Selenium is a trace mineral found naturally in the soil that also appears in certain foods, and there are even small amounts in water. It supports the adrenal and thyroid glands and helps protect cognition. It may also fight off viruses, defend against heart disease and slow down symptoms correlated with other serious conditions like asthma.[51]

Lavender Essential Oil

Lavender oil reduces inflammation and helps the body in many ways, such as producing important antioxidant enzymes - especially glutathione, catalase and superoxide dismutase.[52]

Chlorophyll

Chlorophyll is very helpful for detoxification and linked to natural cancer prevention, blocking carcinogenic effects within the body, and protecting DNA from damage caused by toxins or stress. It's found in things like spirulina, leafy green veggies, certain powdered green juices and blue-green algae.[53]

Frankincense Essential Oil

Frankincense oil has been clinically shown to be a vital treatment for various forms of cancer, including breast, brain, colon and prostate cancers. Frankincense has the ability to help regulate cellular epigenetic function, which positively influences genes to promote healing. Rub frankincense essential oil on your body (neck area) three times daily, and take three drops internally in eight ounces of water three times daily as part of a natural prevention plan.

Health benefits of antioxidants

1. Slow the Effects of Aging by Reducing Free Radical Damage.
2. Protect Vision and the Eyes.
3. Reduce the Effects of Aging on the Skin.
4. Help Prevent Stroke and Heart Disease.
5. May Help Decrease Risk of Cancer.
6. Can Help Prevent Cognitive Decline, Such as Dementia or Alzheimer's Disease.
7. Prevent or treat reperfusion injury.

Pharmacological activity of antioxidants

Antioxidants and prevention of atherosclerosis

Lipoprotein oxidation is a key early stage in the development of atherosclerosis. Oxidized LDL is known to promote atherogenesis through foam cell formation and inflammatory responses. Free radicals have been implicated in the oxidative modification of LDL and several basic research studies strongly suggest that progression of the atherosclerotic lesions can be delayed by intervention with anti-oxidants.[54]

In a recent randomized, double-blind, placebo-controlled factorial trial of vitamin E and vitamin C, designed by Physicians Health Study II and carried out between 1997 and 2007, neither vitamin C (500 mg daily) nor vitamin E (400 IU daily) could reduce the risk of major cardiovascular events in 14,641 US male physicians with initially age of 50 years or older. During the follow-up (mean of 8 years), there were 1245 confirmed major cardiovascular events. Vitamin E had no effect on the incidence of major cardiovascular events, compared to placebo (both vitamin E and placebo groups, 10.9 events per 1000 person-years; hazard ratio (HR), 1.01 [95% confidence interval (CI), 0.90-1.13]; *P*=0.86), as well as total myocardial infarction (HR, 0.90 [95% CI, 0.75-1.07]; *P*=0.22), total stroke (HR, 1.07 [95% CI, 0.89-1.29]; *P*=0.45), and cardiovascular mortality (HR, 1.07 [95% CI, 0.90-1.28]; *P*=0.43).

Similarly, compared with placebo, vitamin C had no significant effect on major cardiovascular events (in vitamin C and placebo groups, there were 10.8 and 10.9 events per 1000 person-years, respectively; HR,0.99 [95% CI, 0.89-1.11]; *P*=0.91), as well as total myocardial infarction (HR, 1.04 [95% CI, 0.87-1.24]; *P*=0.65), total stroke (HR, 0.89 [95% CI, 0.74-1.07]; *P*=0.21), and cardiovascular mortality (HR, 1.02 [95% CI, 0.85-1.21]; *P*=0.86). Neither vitamin E (HR, 1.07 [95% CI, 0.97-1.18]; *P*=0.15) nor vitamin C (HR, 1.07 [95% CI, 0.97-1.18]; *P*=0.16) had a significant effect on total mortality, however, vitamin E was associated with an increased risk of hemorrhagic stroke (HR, 1.74 [95% CI, 1.04-2.91]).

Antioxidants and prevention of cancer

The underlying cause of cancer is thought to be damage to DNA, much of which is oxidative in nature. These oxidative processes, the mechanisms of which not fully understood, occur during the promotional stage of carcinogenesis. Therefore, it is plausible that antioxidants may be able to interfere with the metabolic activation of chemical carcinogens, cause regression of pre-malignant lesions or inhibit their development into cancer. Although there are many compounds in fruits and vegetables that may potentially influence cancer risk, it is generally assumed that certain antioxidants such as vitamin E, Vitamin C and beta-carotene may be responsible for the lower cancer rates. However, the few randomized trials of vitamin E, vitamin C or beta-caroten supplementation show no overall benefits; some even suggest harm. The findings of recent trials are summarized below:

The Physicians' Health Study II Randomized Controlled Trial also evaluated whether long-term vitamin E (400 IU every other day) or vitamin C (500 mg daily) supplementation decreases the risk of prostate and total cancer events among men. During a mean follow-up of 8.0 years, there were 1943 confirmed incident cases of total cancers and 1008 cases of prostate cancer. Compared with placebo, vitamin E had no effect on the incidence of total cancer (vitamin E and placebo groups, 17.8 and 17.3 cases per 1000 person-years; HR, 1.04; 95% CI, 0.95-1.13; *P*=0.41) or prostate cancer (vitamin E and placebo groups, 9.1 and 9.5 events per 1000 person-years; HR, 0.97; 95% CI, 0.85-1.09; *P*=0.58). There was also no significant effect of vitamin C on total cancer (vitamin C and placebo groups, 17.6 and 17.5 events per 1000 person-years; HR, 1.01; 95%CI, 0.92-1.10; *P*=0.86) or prostate cancer (vitamin C and placebo groups, 9.4 and 9.2 cases per 1000 person-years; HR, 1.02; 95% CI, 0.90-1.15; *P*=0.80). Neither vitamin E nor vitamin C had a significant effect on colorectal, lung, or other site-specific cancers. Stratification by various cancer risk factors demonstrated no significant modification of the effect of vitamin E on prostate cancer risk or either supplement on total cancer risk. In this large, long-term trial neither vitamin E nor vitamin C supplementation reduced the risk of prostate or total cancer in middle-aged and older men.

Antioxidants and prevention of ocular disease

Oxidative processes are thought to be an important contributing factor in the development of both cataracts and the age-related disorder of the retina, maculopathy. Oxidation, induced mainly by exposure to UV light, is believed to be a major cause of damage to the proteins of the lens. The oxidized protein precipitates and causes cloudiness of the lens. Antioxidants and antioxidant enzymes inactivate harmful free radicals and proteases degradation and remove the damaged portion from the lens, but the oxidative damage occurs at a faster rate. The oxidized protein may therefore accumulate, and with time, the damage becomes irreversible.

There is substantial interest in determining whether antioxidant lower risks of cataract development and progression. Basic laboratory studies and observational epidemiologic studies in humans support this possibility. Supplementation with antioxidant vitamins and minerals prevents or delays cataract development *in vitro* and in animal models. Individuals with higher intakes of fruits and vegetables, or higher plasma levels of various antioxidant nutrients, tend to have lower risks of cataract. However, the data for individual nutrients, including vitamins C and E and the carotenoids, are inconsistent. Rrecent randomized trials have found vitamin E and C ineffective against cataract.

Another randomized, double-blind, placebo-controlled clinical trial evaluated the effect of a multivitamin/mineral supplement on the development or progression of age-related lens opacities. Participants (n = 1,020) aged 55 to 75 years and with early or no cataract, were randomly assigned to a daily tablet of multivitamin/mineral formulation (including vitamin A 5000 IU, vitamin C 60 mg, and vitamin E 30 IU) or a placebo and were observed for an average of 9.0 ± 2.4 years.

Compared with placebo, total lens events were less common in participants who took the multivitamin/mineral formulation, but treat-ment had opposite effects on the development or progression of nuclear and posterior subcapsular cataract opacities, the two most visually important opacity subtypes. No statistically significant treatment effects were seen for cortical opacities, moderate visual acuity loss, or cataract surgery.

Antioxidants and prevention of skin aging

The reactions which add hydroxyl groups to the amino acids proline and lysine in the collagen molecule, via prolylhydroxylase and lysyl hydroxylase, both require vitamin C as a cofactor. Hydroxylation allows the collagen molecule to assume its triple helix structure, making vitamin C essential to the development and maintenance of scar tissue, blood vessels, and cartilage. In addition, topically applied vitamin C seems to enhance the mRNA level of collagens I and III, their processing enzymes, and the tissue inhibitor of matrix metalloproteinase 1 in the human dermis.

A double-blind randomized trial was performed to evaluate the clinical effects of a cream containing vitamin C vs. excipient on photoaged skin. Twenty healthy French female volunteers aged 51-59 years presenting with photoaged skin were given a topically applied cream containing 5% vitamin C and its excipient on their low-neck and arms over a 6-month period in view to evaluate efficacy and safety of such treatment. Clinical assessments included evaluation at the beginning and after 3 and 6 months of daily treatment. Cutaneous biopsies were obtained at the end of the trial and examined using immunohistochemistry and electron microscopy. Clinical examination by a dermatologist and self-assessment by the volunteers demonstrated a significant improvement, in terms of the 'global score', on the vitamin C-treated side compared with the placebo. The study reported a highly significant increase in the density of skin microrelief and a decrease of the deep furrows. Ultrastructural evidence of the elastic tissue repair was also obtained and confirmed the favorable results of the clinical and skin surface examinations.[55]

Mechanism of Antioxidants

Enzymatic antioxidants and nonenzymatic antioxidants modulate the free radical reactions. Body protects itself from ROS by using enzymatic antioxidant mechanisms. The antioxidant enzymes reduce the levels of lipid hydroperoxide and H_2O_2, thus they are important in the prevention of lipid peroxidation and maintaining the structure and function of cell membranes. Examples of the enzymatic antioxidants are CAT, GSHPx, SOD, and peroxiredoxin I-IV (I-IV).

$$2H_2O_2 \xrightarrow{catalase} 2H_2O + O_2$$

$$\mathrm{ROOH} + 2\mathrm{GSH} \xrightarrow{\mathrm{GSHP_x}} \mathrm{ROH} + \mathrm{GSSG}$$

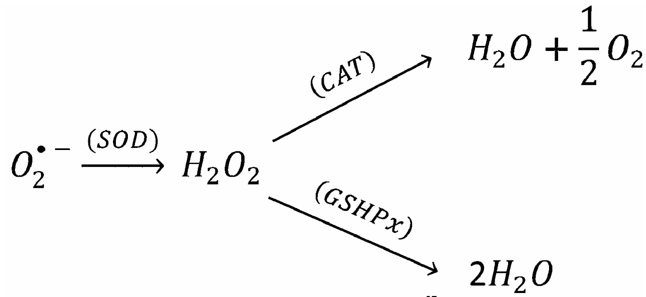

Fig 10 mechanism of ROS[57]

Vitamin C or ascorbic acid, is a water-soluble free radical scavenger. Moreover, it regenerates vitamin E in cell membranes in combination with GSH or compounds capable of donating reducing equivalents. The general mechanism of vitamin c is given below

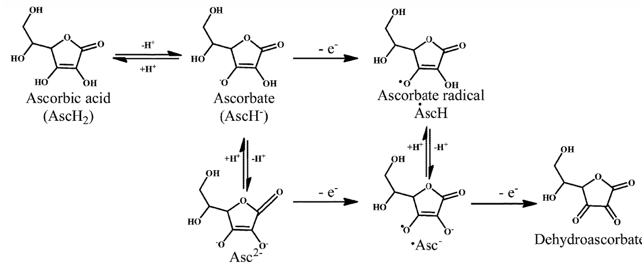

Fig 11 Mechanism of radical scavenging activity of ascorbic acid

Antioxidant potential of vitamin A was first described by Monaghan and Schmitt, who reported that vitamin A can protect lipids against rancidity. Vitamin A has a vital antioxidant contribution in protecting human LDL against copper-stimulated oxidation. The general mechanism of vitamin A is given below.

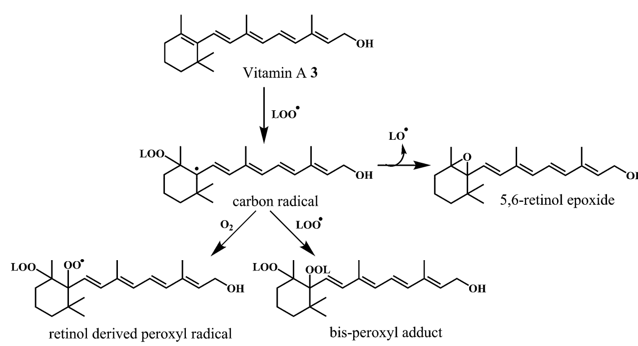

Fig 12 Mechanism of radical scavenging activity of vitamin A[58]

Quercetin is a flavonol, known to protect DNA from oxidative damage resulting from the attack of $^{\bullet}OH$, H_2O_2, and $O_2^{\bullet-}$ on the DNA oligonucleotides. According to the reports, quercetin has opposite effects on DNA damage induced by cupric ion depending on the concentration of cupric ion. At the low concentration of cupric ions (≤25 μM), quercetin exhibit a protective role. While, at higher concentration of cupric ion (≥25 μM), quercetin enhances the damage to DNA by ROS.

Table 3 Enzymatic antioxidants, their cellular locations and the reactions they carry out[56]

Enzymatic antioxidant	Cellular location	Substrate	Reaction
Mn/Cu/Zn SOD	Mitochondrial matrix (Mn SOD) cytosol (Cu/Zn SOD)	$O_2^{\bullet-}$	$O_2^{\bullet-} \rightarrow H_2O_2$
CAT	Peroxisomes cytosol	H_2O_2	$2H_2O_2 \rightarrow O_2 + H_2O$
GSHPx	Cytosol	H_2O_2	$H_2O_2 + GSH \rightarrow GSSG + H_2O$
Prx–I	Cytosol	H_2O_2	$H_2O_2 + TrxS_2 \rightarrow Trx(SH)_2 + H_2O$

Therefore, it is very important to consider the concentration of the chelating metal ions, such as copper or iron while evaluating the protective or degenerative effects of quercetin and other bioflavonoids. The general mechanism of Quercetin is given below.

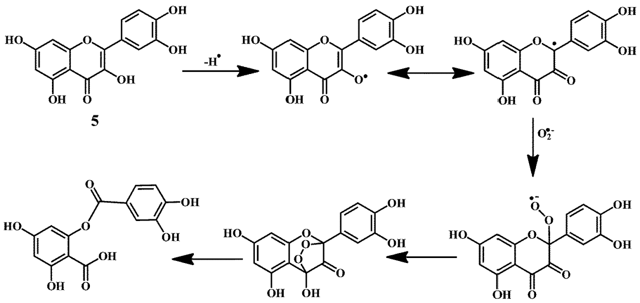

Fig 13 Mechanism of superoxide anion radical scavenging activity of quercetin[59]

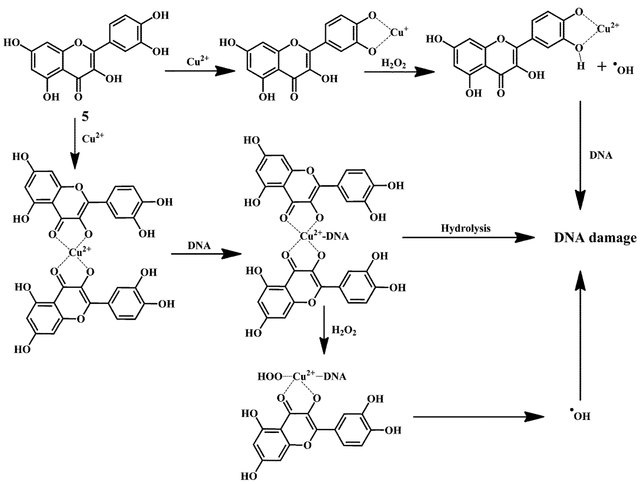

Fig 14 Mechanism of DNA damage induced by quercetin copper complex.[60]

SOD is an antioxidant enzyme involved in scavenging the ROS. There are several classes of SOD, which include intracellular copper, zinc SOD (Cu, Zn SOD/SOD_1), mitochondrial manganese SOD (Mn SOD/SOD_2), and extracellular Cu, Zn SOD (EC SOD/SOD_3).The method for the evaluation of the $O_2^{\cdot -}$ scavenging activity of antioxidants is explained here by using PMS-NADH-NBT system, which is composed of *N*-methylphenazinemethosulphate (PMS), nitrobluetetrazolium chloride (NBT), and NADH (a reduced form of nicotineamide-adenine-dinucleotide). The general mechanism of SOD is given below.

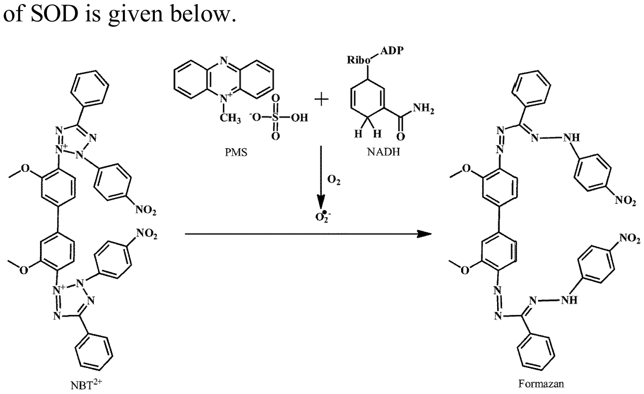

Fig 15 Reduction of NBT by superoxide anion radical produced in PMS-NADH reaction.[61]

Total reactive oxygen potential (TRAP) and total antioxidant reactivity (TAR) are measured by using Luminol enhanced chemiluminescence. When the luminol is allowed to react with the free radical source, a steady chemiluminescence is observed that can be directly correlated to the rate of luminol oxidation. The addition of free radical scavengers reduces the chemiluminescence intensity. The effect of antioxidants on the induced chemiluminescence intensity of luminol by radicals derived from the thermolysis of 2,2′-azobis-2-amidinopropanedihydrochloride (AAPH) can be employed to monitor the TRAP and TAR levels. The mechanism of action is given below.

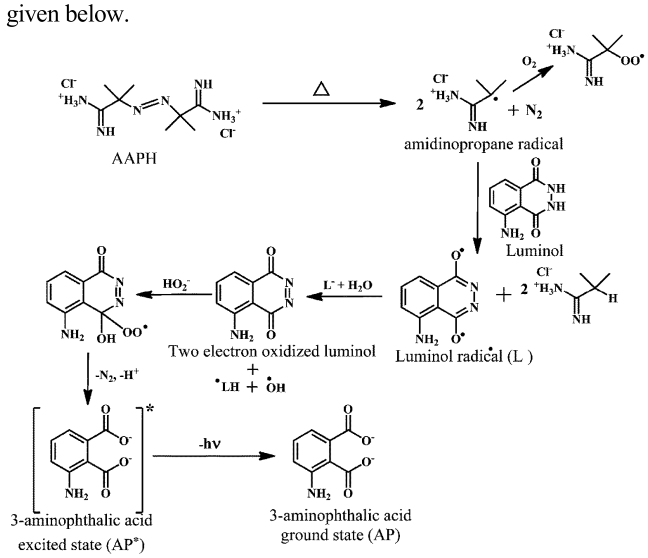

Fig 16 Mechanism of AAPH induced chemiluminescence of luminol

Overdose of antioxidants

Most of the antioxidants are water-soluble, meaning that any excess consumed can be quickly and easily excreted by the body. But vitamins A and E, are fat-soluble, meaning that excess intake is harder to excrete and will be stored within fat cells. This can lead to an overdose condition that is extremely dangerous. But practically it is impossible to overdose on these nutrients from food alone. It's when they are added in the form of supplements that this becomes a real threat. While you technically cannot overdose on antioxidants such as vitamin C, continuous high intake can lead to a saturation effect that is detrimental to your health. This is because the human body requires a level of oxidant activity for normal, healthy function, including hormonal activity, such as the production of testosterone and cellular respiration, or the production of energy. Saturation with antioxidants hinders these systems.[62]

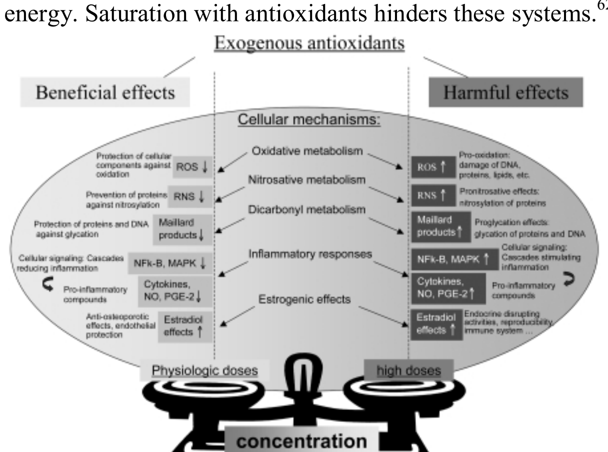

Fig 17 Overdose of antioxidants and its effects

CONCLUSION

In the world of molecules, antioxidants are true superheroes. antioxidants are so important, we need to get acquainted with their enemies: Free Radicals. They are our bodies' first line of defense against free radicals, which are unstable molecules. Several decades of research findings suggested that consuming greater amounts of antioxidant-rich foods might help to protect against diseases. Because of these results, there has been a lot of research on antioxidant supplements. High levels of antioxidants in the body are probably beneficial. There are thousands of different nutrients which acts as antioxidants. The enormous amount of research on antioxidants is incredibly confusing. In future, it is possible that consumers will become more willing to accept safe synthetic antioxidants as a alternative to natural antioxidants. The reported evidence suggest that dietary antioxidants helps in disease prevention. The scope of this article is limited to the essential role and importance of antioxidants.

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